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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,117	02/22/2006	Richard L. Miller	58751US010	2906

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,117	MILLER ET AL.	
	Examiner	Art Unit	
	BONG-SOOK BAEK	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11,14,17,20-22,27,34 and 36* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7, 8, 11, 14, 17, 20-22, 27, 34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's submission filed August 10, 2009 has been received and entered into the present application.

The amendment filed on August 10, 2009 is acknowledged. Claims 1-8, 11, 14, 17, 20-22, 27, 34, and 36 are pending.

Applicants' arguments, filed on August 10, 2009, have been fully considered but they are moot in view of new grounds of rejections. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 7, 8, 11, 14, 17, 20-22, 27, 34 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention. All dependent claims are included in this rejection.

Independent claim 1 recites "a method of delivering an immune response modifier (IRM) compound to a mucosal surface so as to achieve immunomodulation with reduced irritation, comprising: interrupted delivery of an IRM compound other than imiquimod by intermittently applying the IRM to the mucosal surface and, after each application, removing from the mucosal surface at least 50% by weight of the IRM that was originally applied at a time before it would otherwise be naturally absorbed or eliminated". The limitation "reduced irritation" is unclear because it does not specify "a basis to compare" (i.e., irritation is reduced compared to what?) and a cause and place of irritation (i.e., Is irritation caused by the IRM compound, the delivery device or the existing condition such as infection and does irritation mean irritation of mucosal surface, irritation of stomach or irritation of feeling?). In addition, it is unclear what Applicant mean by "intermittently applying". Does this mean one application followed by removing or repeated applications (multiple application followed by removing)? If "intermittently applying" means repeated applications, the same applicator with leftover IRM compound will be reapplied or a new one will be applied? If the same applicator with leftover IRM compound is reapplied, is "the IRM that was originally applied" referring to the initial amount of the IRM, which is applied at the beginning, or the amount of the IRM which is applied right before removing?

Claim 2 recites the limitations "the same device". There is a lack of antecedent basis for this limitation in the claim because claim 1 does not utilize the language of the limitation "said device". In addition, it does not specify the same device as what.

Claims 8 and 11 recites "a substantial amount of the IRM". The term "substantial" is a relative term, which renders the claim indefinite. The term "substantial" is not defined by the claim and the specification does not provide a standard for ascertaining the requisite degree. If when defined by the Merriam-Webster's dictionary it means "being largely but not wholly that which is specified", it is unclear how much is substantial amount. Thus, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection desired as to this term. In addition, claim 1 recites "removing from the mucosal surface at least 50% by weight of the IRM that was originally applied". It is unclear whether claims 8 and 11 further limit claim 1 since the substantial amount can be any "substantial" amount such as 40% or 45%.

Independent claim 27 recites "a method of treating a condition associated with a mucosal surface with an immune response modifier (IRM) compound and reducing irritation caused by the IRM, comprising: interrupted delivery of an IRM compound other than imiquimod by intermittently applying the IRM to the affected for a time sufficient to achieve therapeutic immunomodulation and, after each application, removing from the mucosal surface at least 50% by weight of the IRM that was originally applied at a time before it would otherwise be naturally absorbed or eliminated". The limitation "reducing irritation" is unclear because it does not specify "a basis to compare" (i.e., irritation is reduced compared to what?) and a place of irritation (i.e., does irritation mean irritation of mucosal surface, irritation of stomach or irritation of feeling?). In addition, it is unclear what Applicant mean by "intermittently applying". Does this mean one application followed by removing or repeated applications (multiple application followed by removing)? If "intermittently applying" means repeated applications, the same applicator with leftover IRM compound will be reapplied or a new one will be applied? If the

same applicator with leftover IRM compound is reapplied, is "the IRM that was originally applied" referring to the initial amount of the IRM, which is applied at the beginning, or the amount of the IRM which is applied right before removing? Also, if it means one application followed by removing, how they administer a therapeutically effective amount for achieving immunomodulation by removing at least 50% of the original amount, which means up to 100% can be removed?

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7, 8, 11, 14, 17, 20-22, 27, 34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for removing from the mucosal surface at least 50% by weight of the IRM when a delivering device is a tampon, a cervical cap, a diaphragm, a cotton swab, a cotton sponge, and a foam sponge, does not reasonably provide enablement for other delivering devices such as suppository. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or

unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All factors have been considered together and specifically relevant factors are addressed below:

The nature of the invention. The claims are drawn to a method of delivering an immune response modifier (IRM) compound to a mucosal surface so as to achieve immunomodulation with reduced irritation, comprising: interrupted delivery of an IRM compound other than imiquimod by intermittently applying the IRM to the mucosal surface and, after each application, removing from the mucosal surface at least 50% by weight of the IRM that was originally applied at a time before it would otherwise be naturally absorbed or eliminated, using any delivering device such as a tampon, a cervical cap, a diaphragm, a cotton swab, a cotton sponge, a foam sponge, and a suppository .

The state of the prior art:

A suppository is a drug delivery system that is inserted into the rectum (rectal suppository), vagina (vaginal suppository), or urethra (urethral suppository), where it dissolves. The general principle is that the suppository is inserted as a solid, and will dissolve inside the body to deliver the medicine. Thus, it is not possible to remove at least 50% by weight of the IRM once applied since the suppository melts away. In addition, claim 2 recites the IRM is applied and removed with the same device. How can the IRM be removed with the same device when the device is gone? Thus, one having ordinary skilled would not know how to practice the clamed method when the delivering device is a suppository or similar devices.

The Presence or Absence of Working Examples: The specification provides some examples using cotton devices. However, in the specification, there is no example using a suppository or or similar devices.

The Quantity of Experimentation Needed. As stated above, the skilled artisan would not accept the assertion that the instantly claimed method could be predictably practiced by using any delivering device as inferred in the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4, 7, 8, 11, 14, 17, 20-22, 27, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0058674 in view of WO 99/29693 in further view of US patent 6,328,991).

US 2002/0058674 teaches method/system for treating condition associated with a mucosal surface, the system comprising an immune response modifier (IRM) compound chosen from imidazoquinoline amines, imidazopyridine amines, 6,7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, oxazoloquinoline amines, thiazoloquinoline amines, 1,2-bridged imidazoquinoline amines, and pharmaceutically acceptable salts thereof and an applicator device for applying the IRM compound to the mucosal surface, wherein this system of IRM compounds and applicator is used to treat conditions associated with mucosal surfaces such as cervical dysphasia and cervical intraepithelial neoplasia (abstract). The reference further discloses the structure of imidazonaphthyridine amines of formula X, which embraces the elected compound and the disclosure of WO99/29693, which teaches the same imidazonaphthyridine amines structure as the formula X and the elected compound, is incorporated by reference ([0004] and [0179]-[0246]). It discloses the use of imiquimod in their example formulation Table 1 [0351] and Table 2 [0354]. However, the language comprising in their claim 1 enables one skilled in the art to use any immune response modulators listed in the disclosure for the same purpose and particularly advantageous for topical application to the cervix for treatment of cervical conditions such as cervical dysplasias including dysplasia associated with human papillomavirus (HPV) ([0002]).

US 2002/0058674 further teaches that IRM can be formulated as a suppository and administered intravaginally using a suppository applicator [0343] or IRM can be topically

applied to the cervical mucosa by using a direct cervical applicator, as previously described or using a cervical cap ([0334]). This reads on instant claim 2 because it uses the same device to apply and when the device is removed after use it is removed from the same device. The reference further teaches that the applicator device is prefilled with a therapeutically effective amount of the IRM compound (claim 26), which reads on the limitation "the IRM is predispersed within a solid matrix capable of releasing the IRM" recited in the instant claim 34. US 2002/0058674 teaches that single dose, randomized, double-blind, placebo controlled dose escalation study which evaluated five doses of imiquimod. 50, 100, 150, 200 and 250 mg of imiquimod in a cream formulation were applied to the cervix for eight hours ([0348]). '674 further teaches that although some of the beneficial effects of IRMs are known, the ability to provide therapeutic benefit via topical application of an IRM for treatment of a particular condition at a particular location may be hindered due to tissue irritation, formulation wash away, poor permeation or undesired systemic delivery of the topically applied compound. Accordingly, there is a need for new methods, formulations, and systems to provide the greatest therapeutic benefit from this class of compounds ([0007]). This explains the limitation of claim 1 that the method of treatment should achieve immuno modulation with reduced irritation, and the disposable tampon's and cervical cup explained above.

US 2002/0058674 also teaches topical administration of a pharmacological agent to a tissue surface can provide localized therapeutic benefit without concomitant systemic effects. However, topical application is often difficult or impossible due to the anatomical location of the tissue. In some cases, application of the agent to a general anatomical region that includes or surrounds the target tissue may be an alternative to direct topical application. But, if the

agent has irritating properties, this alternative disadvantageously carries with it the possibility of irritating tissues surrounding the target tissue. In addition, even if the agent is non-irritating, regional application typically requires use of a greater volume or concentration of the agent to achieve a therapeutic result equivalent to that achieved by direct application to the target tissue ([0008]).

US 2002/0058674 further teaches that the uterine cervix is one example of a target tissue to which it is difficult to apply a topical agent. Relative to a standing position, the cervix is typically located at the uppermost portion of the vaginal cavity. However, while the cervix is located at the uppermost portion of the vaginal cavity, age, the stage of the estrous cycle, pregnancy, and other factors cause variability of the location of the cervix between different women and in the same woman at different stages of life ([0009]). In addition, with the exception of certain body orientations, gravity tends to drain agents away from the cervix. Normal discharge and flow of fluids, both menstrual and non-menstrual, also drain away from the cervix. Thus, any applicator that is not capable of repeatedly delivering an appropriate amount of agent to the uppermost end of the vaginal cavity risks less than optimal treatment ([0011]). Although '674 does not teach the removal of the device after two hours as in instant claim 11, one skilled in the art would have reasoned that the use of cervical cap or other applicators depending on the state of life of the women's body it can be removed and inserted within this time period.

'674 does not specifically disclose 1-(2-methylpropyl)-IH- imidazo [4,5-c] [1,5]naphthyridin-4-amine, the elected specie of the current invention although the generic imidazonaphthyridine amines disclosed in the reference encompasses the elected species. Also,

it is silent about "removing at least 50% by weight of the IRM that was originally applied at a time before it would otherwise be naturally absorbed or eliminated" and "activating a TLR such as TRL-7".

WO 99/29693 teaches that 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5] naphthyridin-4-amine, which is a species of imidazonaphthyridine compounds of the same formula as disclosed in '674 reference, has immune response modifying effects and is useful for treating viral diseases and tumors such as cervical intraepithelial neoplasia and human papillomavirus and associated neoplasia (claim 1, p47, example 30, and p26, lines 3-20, lines 3, p36, lines 14-19, and claims 1-7).

US patent 6,328,991 teaches a removable vaginal device such as vaginal sponge impregnated with a solution containing a carrier and an active pharmaceutical agent for vaginal infections, which releases active agents throughout the vaginal canal while being inserted and is removed (abstract, column 4, lines 40-57, and column 6, lines 1-64). US 4393871 also teaches a vaginal device adapted for insertion and placement in the human vaginal cavity and subsequent removal therefrom for the administration of a variety of medications such as anti-infectives, anti-inflammatories, estrogens, progestogens, and the like (abstract). It also teaches that the amount of active agent incorporated in the vaginal device of the present invention varies, depending on the particular active agent, and the desired therapeutic or prophylactic therapy and the upper limit and the lower limit will depend on the activity of the active agent and the time span of its release from the device. It further teaches that the concentration of active pharmaceutical in such excess amount represents the desired concentration in the dosage to be released and the amount of excess liquid is dependent upon the molecular weight of the active and the nature of the

active, e.g. its molecular weight. In addition, it teaches that the lower the molecular weight, the less liquid is required. The more compatible the molecular structure of the active with the vaginal tissue, the less active is required.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the elected compound 1-(2-methylpropyl)-lH- imidazo [4,5-c] [1,5] naphthyridin-4-amine for the method of '674 since '674 already discloses imidazonaphthyridine amines derivatives encompassing the elected compound and WO 99/29693 teaches that 1-(2-methylpropyl)-lH-imidazo [4,5-c] [1,5] naphthyridin-4-amine is a species of imidazonaphthyridine derivatives, which is useful for treating viral diseases and tumors such as cervical intraepithelial neoplasia and human papillomavirus and associated neoplasia. One of ordinary skill in the art would have been motivated to select the elected compound from the genus in the reference, since such compounds would have been suggested by the reference as a whole because the skilled chemist would have the reasonable expectation that any of the species of the genus would have similar properties and thus, the same use as taught for the genus as a whole i.e., as IRM compound for treating cervical dysplasia by applying it locally with either suppository or cervical cap as taught by '674.

With regard to "activating a TLR such as TRL-7", it would be expected features since the reference teaches the same compound as the elected species. It is noted that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). When the claimed and prior art products are

identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). Alternately, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. See Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

With regard to "removing at least 50% by weight of the IRM that was originally applied at a time before it would otherwise be naturally absorbed or eliminated" and "removing 2 hours or less after it is applied", the use of removable cervical devices for delivering an IRM drug to a mucosal surface within vagina would have been obvious to one of ordinary skill in the art at the time the invention was made as taught by the cited references and one skilled in the art would have known that the device could be removed after insertion within a certain time period and the substantial amount of the drug applied to the device, which is not absorbed by mucosal surface, would be removed along with the device. Furthermore, the cited references teach that excess amount of an active compound is usually applied to the applicator for achieving the desired concentration to be released and the amount of excess liquid is dependent upon the desired therapeutic or prophylactic therapy and the molecular weight of the active and the nature of the active, e.g. its molecular weight. Thus, one of ordinary skill in the art would have been motivated to remove the excess amount by taking out the device in order to avoid overdosing or other side

effects such as irritation. The amount removed and the duration of application will be adjusted based on the particular active agent and the desired therapeutic or prophylactic therapy. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of the duration of period and the amount removed would have been obvious at the time of applicant's invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 8:00-5:00 Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-071818. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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